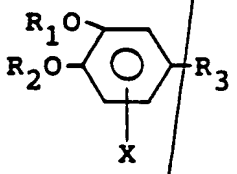
add B12

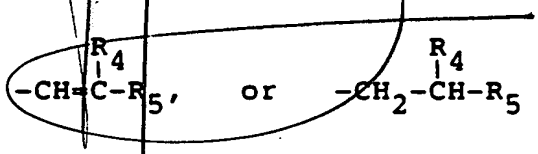
What is claimed is:

1. Pharmacologically active catechol derivatives of formula I



I

wherein R_1 and R_2 independently comprise hydrogen, alkyl, optionally substituted acyl, optionally substituted aroyl, lower alkylsulfonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group, X comprises electronegative substituent such as halogen, nitro, cyano, lower alkylsulfonyl, sulfonamido, trifluoromethyl, aldehyde or carboxyl and R_3 comprises hydrogen, halogen, substituted alkyl, hydroxyalkyl, nitro, cyano, optionally substituted amino, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidenecarbonyl or carboxyl group or a group selected from

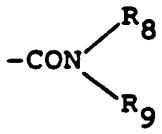


wherein R_4 comprises hydrogen, alkyl, amino, cyano, carboxyl or acyl and R_5 comprises hydrogen, amino, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl, COZ, wherein Z is an optionally substituted heterocyclic ring or one of following optionally substituted groups; carboxamido, carbamoyl, aroyl or heteroaryl or R_4 and R_5 together form a five to seven membered substituted cycloalkanone ring;

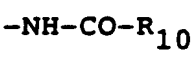
$$-(CO)_n(CH_2)_m-COR$$

wherein n is 0-1, m is 0-7 and R comprises alkyl, hydroxy,

carboxyalkyl, optionally substituted alkene, optionally substituted heterocyclic ring, alkoxy or substituted amino;



wherein R_8 and R_9 independently comprise hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or taken together form an optionally substituted piperidyl group;



wherein R_{10} comprises a substituted alkyl group.

2. A compound as claimed in claim 1, wherein the compound is 3,4-dihydroxy-5-nitro-ω,ω-dicyanostyrene.

3. A compound as claimed in claim 1, wherein the compound is 4-(3,4-dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-one.

4. A compound as claimed in claim 1, wherein the compound is 3-(3,4-dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one.

5. A compound as claimed in claim 1, wherein the compound is 3-(3,4-dihydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one.

6. A compound as claimed in claim 1, wherein the compound is N-methyl-N-propargyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic acid amide.

7. A compound as claimed in claim 1, wherein the compound is 4-(3,4-dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-ol.

8. A compound as claimed in claim 1, wherein the compound is N-(1-adamantyl)-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic acid amide.

9. A compound as claimed in claim 1, wherein the compound is N-isopropyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic acid amide.

10. A compound as claimed in claim 1, wherein the compound is 4-hydroxy-3-methoxy-5-nitrocinnamic acid.

11. A compound as claimed in claim 1, wherein the compound is 5-(3,4-dihydroxy-5-nitrophenyl)pentanoic acid.

12. A compound as claimed in claim 1, wherein the compound is 2,5-bis-(3,4-dihydroxy-5-nitrobenzylidene)cyclopentanone.

13. A compound as claimed in claim 1, wherein the compound is 2-propionyloxy-6-nitrophenol.

14. A compound as claimed in claim 1, wherein the compound is 1,2-diacetoxy-3,5-dinitrobenzene.

15. A compound as claimed in claim 1, wherein the compound is 3',4'-dihydroxy-5'-nitroacetophenone.

16. A compound as claimed in claim 1, wherein the compound is 3,4-dihydroxy-5-nitrobenzaldehyde.

17. A compound as claimed in claim 1, wherein the compound is 3,4-dihydroxy-5-nitrobenzonitrile.

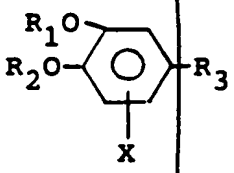
18. A compound as claimed in claim 1, wherein the compound is 4-chloro-6-nitrocatechol.

19. A compound as claimed in claim 1, wherein the compound is 1,2-dipropionyloxy-3,5-dinitrobenzene.

20. A compound as claimed in claim 1, wherein the compound is 2-pivaloyloxy-4,6-dinitrophenol.

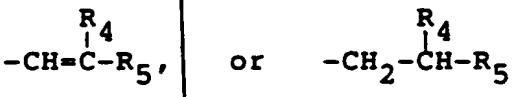
21. A compound as claimed in claim 1, wherein ythe compound is 3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentanedione.

22. A method for the preparation of new pharmacologically active catechol derivatives of the formula



I

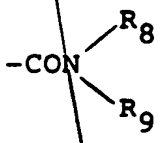
wherein R_1 and R_2 independently comprise hydrogen, alkyl, optionally substituted acyl, optionally substituted aroyl, lower alkylsulfonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group, X comprises electronegative substituent such as halogen, nitro, cyano, lower alkylsulfonyl, sulfonamido, trifluoromethyl, aldehyde or carboxyl and R_3 comprises hydrogen, halogen, substituted alkyl, hydroxyalkyl, nitro, cyano, optionally substituted amino, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidenecarbonyl or carboxyl group or a group selected from



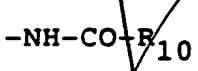
wherein R_4 comprises hydrogen, alkyl, amino, cyano, carboxyl or acyl and R_5 comprises hydrogen, amino, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl, COZ, wherein Z is an optionally substitutted heterocyclic ring or one of following optionally substituted groups; carboxamido, carbamoyl, aroyl or heteroaryl or R_4 and R_5 together form a five to seven membered substituted cycloalkanone ring;

wherein n is 0-1, m is 0-7 and R comprises alkyl, hydroxy,

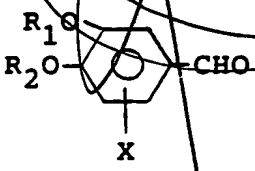
carboxyalkyl, optionally substituted alkene, optionally substituted heterocyclic ring, alkoxy or substituted amino;



wherein R_8 and R_9 independently comprise hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or taken together form an optionally substituted piperidyl group;

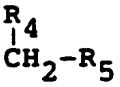


wherein R_{10} comprises a substituted alkyl group, wherein the method comprises an acid or base catalyzed condensation reaction of a compound of formula II



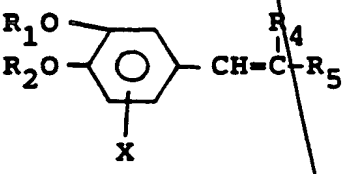
II

wherein R_1, R_2 and X are as defined above, with a compound of formula III



III

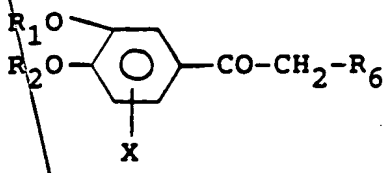
having an active methyl or methylene group and wherein R_4 and R_5 are as defined above to give the compounds of formula Ia



Ia

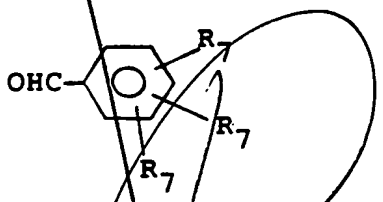
wherein the substituents are as defined above and wherefrom the double bond optionally may be reduced to a single bond;

or a ketone of formula IV



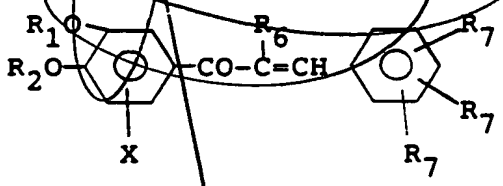
IV

wherein R_1, R_2 and X are as defined above and R_6 is hydrogen or alkyl, is condensed with an aldehyde of formula V



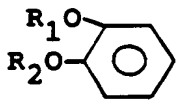
V

wherein R_7 comprises hydrogen, alkyl, alkoxy or dialkylamino to give compounds of formula Ib



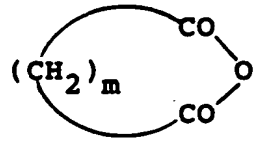
Ib

wherein R_1, R_2, X, R_6 and R_7 are as defined above;
or a compound of formula VI



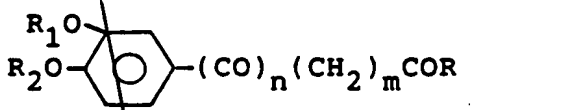
VI

wherein R_1 and R_2 are as defined above is allowed to react with a cyclic acid anhydride of formula VII



VII

wherein m is 1-7 or with a dicarboxylic acid ester chloride of formula VIII

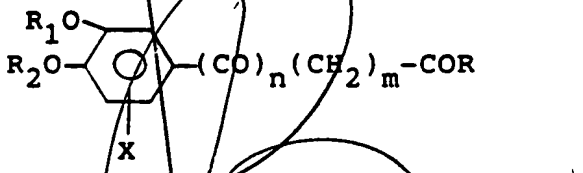


VIII

wherein m is 0-7 and n is 0-1 and R is as defined above and Hal is a halogen atom to give the compounds of formula IX

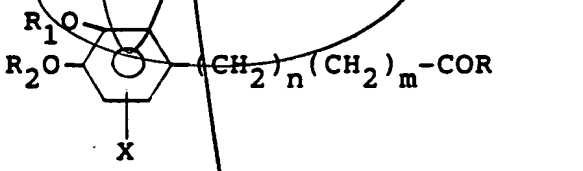
IX

wherein the aromatic ring will be substituted with the group X to give compounds of formula Ic



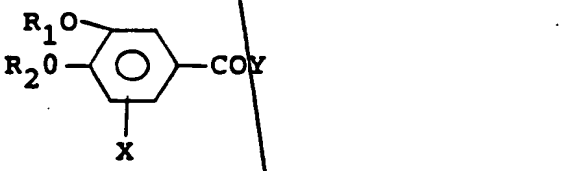
Ic

which compound may be reduced to give compounds of formula Id;



Id

or by allowing a compound of formula X

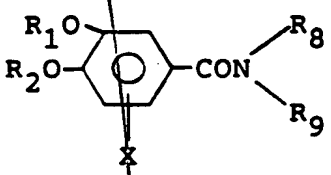


X

wherein R_1 and R_2 are as defined above and Y comprises halogen or another activated group to react with an amine of formula XI

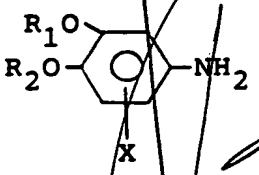
XI

wherein R_8 and R_9 are as defined above to give compounds of formula Ie



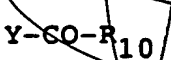
Ie

wherein R_1, R_2, X, R_8 and R_9 are as defined above;
or by allowing the aniline derivative of formula XII



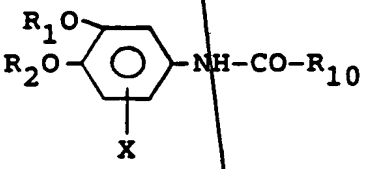
XII

wherein R_1, R_2 and X are as defined above, to react with an activated carboxylic acid derivative of formula XIII,



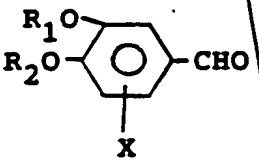
XIII

wherein Y and R_{10} are as defined above to give compounds of formula If



If

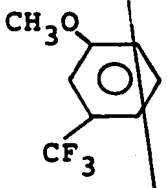
wherein the substituents are as defined above;
or by allowing the compound of formula II



II

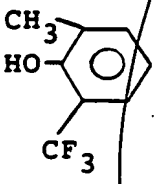
wherein R_1 and R_2 are as defined above and X comprises a halogen atom to react with cuprous cyanide in a polar,

aprotic solvent at elevated temperature or optionally by formylating 2,3-dihydroxybenzonitrile with hexamethylene tetramine to give compounds of formula II, wherein X comprises a cyano group;
or by allowing a compound of formula XIV



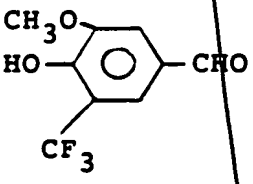
XIV

to react sequentially with butyllithium, trimethylborate and peroxyformic acid to give the compound of formula XV



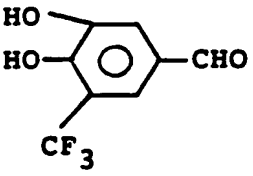
XV

which compound may be formylated with hexamethylenetetramine in fluoroacetic acid to give a compound of formula XVI



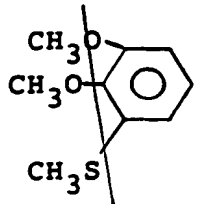
XVI

which compound may be demethylated to the compound of formula XVII;



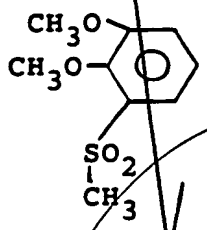
XVII

or by treating the compound of formula XVIII



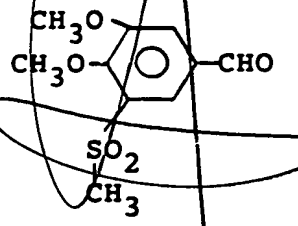
XVIII

with peroxyacetic acid to give the sulfone compound of formula XIX



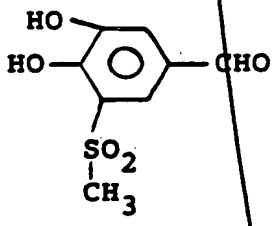
XIX

which compound is formylated to give the compound of formula XX



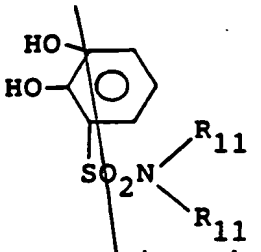
XX

which compound may be demethylated to give the corresponding hydroxy compound of formula XXI;



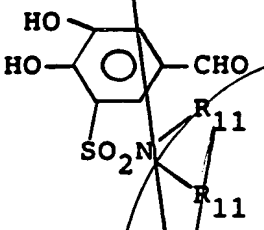
XXI

or by formylation the compound of formula XXII



XXII

wherein R_{11} comprises hydrogen or alkyl, to the compound of formula XXIII



XXIII.

23. A method as claimed in claim 21, wherein the compounds of the formula VI and the formula VIII are allowed to react in the presence of aluminium chloride.

24. A method as claimed in claim 21, wherein the compound of the formula Ic is reduced to a compound of the formula Id by Clemmensen or Wolff-Kischner reduction.

25. A composition in a pharmaceutically acceptable form comprising the compound as claimed in claim 1 as an active ingredient.

26. A composition as claimed in claim 24, comprising the compound as claimed in claim 1, levodopa and optionally a periferic decarboxylase inhibitor.

27. A composition as claimed in claim 24, wherein the periferic decarboxylase inhibitor is carbidopa.

28. A composition as claimed in claim 24, wherein the periferic decarboxylase inhibitor is benzerazide.

add B^{12}

add CH